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## Targeted Gene Editing in the Treatment of X-Linked Hyper-IgM Syndrome

### Grant Award Details

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Targeted Gene Editing in the Treatment of X-Linked Hyper-IgM Syndrome

**Grant Type:** Quest - Discovery Stage Research Projects

**Grant Number:** DISC2-10124

**Project Objective:** To develop a gene-corrected HSC therapy for X-linked Hyper IgM Syndrome; will optimize and compare TALEN and CRISPR based approaches to select candidate for translation.

**Investigator:**

<b>Name:</b>	Caroline Kuo
<b>Institution:</b>	University of California, Los Angeles
<b>Type:</b>	PI

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**Disease Focus:** Blood Disorders

**Award Value:** \$1,512,333

**Status:** Active

### Grant Application Details

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**Application Title:** Targeted Gene Editing in the Treatment of X-Linked Hyper-IgM Syndrome

**Public Abstract:****Research Objective**

We are seeking to develop site-specific hematopoietic stem cell gene therapy with autologous transplant as a definitive treatment option for X-linked Hyper-IgM Syndrome.

**Impact**

These studies would bring stem cell gene therapy for X-HIGM closer to the clinic, as there are currently no options for those without an HLA match or with infections too severe for allogeneic HSCT.

**Major Proposed Activities**

- Identify the optimal CRISPR gRNA, Cas9 variant, and cDNA donor template targeting the CD40L gene.
- Compare TALENs and CRISPR/Cas9 targeting the CD40L gene in terms of their activity, specificity, and ability to allow homology-directed repair in CD34<sup>+</sup> PBSC through short term cultures in vitro.
- Evaluate methods to maximize gene editing and maintain HSC survival and pluripotency.
- Evaluate the efficacy of optimized genome-editing reagents in hematopoietic stem cells long term in vitro in the artificial thymic organoid system and in vivo in NSG mice.
- Assess gene editing of the CD40L gene of X-HIGM patient derived CD34<sup>+</sup> cells using the optimal gene editing platform and reagents determined in Milestones 1-4.

**Statement of Benefit to California:**

Safe, definitive therapies for X-HIGM represent an unmet medical need. Allogeneic stem cell transplant is frequently complicated by graft-versus-host disease and worsening of pre-existing infections. Successful demonstration that stem cell gene therapy can safely and effectively cure X-HIGM will shift the paradigm by which patients will be treated, led by California's position as a leader in the field of gene therapy. This will result in improved patient care in the state and around the world.

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